REMARKS

Claims 1-26 are pending in the application and have been rejected. Claims 2 and 24 have been canceled without prejudice. Claims 1, 3-8, 15, 17-19, 21, 23 and 25-26 have been amended. New claims 27 and 28 have been added.

Support for the amendment to claim 1 can be found in the specification at pages 22 and 28. Claim 3 has been amended to correct dependency. Support for the amendment to claim 4 can be found at pages 31 to 34 of the specification. Support for the amendment to claim 6 can be found in the specification at page 22. Support for the amendment to claim 7 is found in the specification at page 31, lines 2-3. Claims 8 and18 were amended to correct a typographical error, and support for the amendment is in original claims 8 and18 and throughout the specification. Support for the amendment to claim 15 can be found in the specification at pages 9, lines 8-9 and page 17, lines 6-25. Support for the amendments to claims 17, 19, 21 and 23 can be found at page 22 of the specification. Support for the amendment to claim 25 can be found in original claim 23. Support for the amendment to claim 26 can be found in the specification at page 22. Support for new claims 27 and 28 is found in original claim 3. No new matter has been added.

The Office Action acknowledges that Provisional Application 60/210,672 has been reviewed and priority granted.

Please reconsider the Application in light of the following remarks.

I. Objections to the Specification

The Office Action objected to the disclosure because of informalities at pages 2, 5, 8, 14, 15, 16, 18, 19 (lines 2-3 and lines 11-12), 23, 25, 27, 28, 29, 31 38, 39 and 40.

Applicants have amended the specification as suggested by the Examiner to correct typographical errors at pages 2, 5, 8, 14, 16, 18, 19 (lines 2-3 and lines 11-12), 25, 27, 28, 31 38, 39 and 40. Accordingly, these objections to the specification may be properly withdrawn.

The Office Action alleges that at page 15, lines 2-3, which recite "each dimension represents a set of mutually exclusive features from which exactly one is chosen for each candidate model", the meaning of "one is chosen" is not understood.

Applicant has amended the specification at page 15, lines 2-3 to clarify that one mutually exclusive feature is chosen from each set of mutually exclusive features. Support for this amendment can be found in the specification at page 22, line 2, which recites: "First, a set of model feature sets is identified. The user might be interested in including the number of pharmacokinetic compartments in the search. Possible values in this feature set include one compartment, two compartments and three compartments. Any given model will have exactly one of these values, it cannot be both one compartment and two compartment." Therefore, the values one compartment, two compartments and three compartment pharmacokinetics models are mutually exclusive features in the "number of pharmacokinetic compartments" dimension of the candidate search space. Accordingly, this objection to page 22, line 2 of the specification may be properly withdrawn.

The Office Action objects to the specification at page 23, lines 8-9, stating that "If the matrix is diagonal ... then the diagonal elements are simply the *inter* subject variance' appears to be incorrect and it appears that it should be 'if the matrix is diagonal . . . then the diagonal elements are simply the *intra* subject variance".

Applicant respectfully traverses this objection to the specification, as *inter* subject variance is the intended meaning, rather than *intra* subject variance. *Inter* subject variance is intended to have its normal meaning as used in the art, and refers to the variance between subjects in a population of subjects. Accordingly, the objection to the specification at page 23, lines 8-9 may be properly withdrawn.

The Office Action objects to the specification at page 29, lines 2-3, which recites "twice the value of the standard error of estimate from some null value if the p value is to be <0.05." The Office Action asks "what is p here".

Applicants respectfully traverse this objection to the specification. The term "p value" is well recognized in the art of statistics. For example, the term "p value" is defined in well recognized introductory statistics text as:

> "The observed significance level, or p-value, for a specific statistical test is the probability (assuming H_o is true) of observing a value of the test statistic that is at least as contradictory to the null hypothesis, and supportive of the alternative hypothesis, as the one computed from the sample data."

(A First Course in Statistics, 2nd Ed., McClave et al., Dellen Publishing Co., San Fransciso, CA (1986), Definition 6.3, page 246; attached as Appendix A). Accordingly, the objection to the specification at page 29, lines 2-3 may be properly withdrawn.

II. Objections to the Claims

Claim 6 was objected to for reciting "from which exactly is chosen for each candidate model and each model is represented by a bit string". The Examiner has suggested amending claim 6 to recite "from which exactly one is chosen for each candidate model and each model is represented by a bit string."

Applicant has amended claim 6 to clarify that "exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model and each model is represented by a bit string". Accordingly, the objection to claim 6 may be properly withdrawn.

Claim 18 was objected to for reciting "interinOdividual" Applicants have amended claim 18 to recite "interindividual". Accordingly, the objection to claim 18 may be properly withdrawn.

III. The Claims Meet the Requirements of 35 U.S.C. § 112, First Paragraph.

Claims 1-4 and 6-26 stand rejected under 35 U.S.C. § 112, first paragraph, for "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention." (Office Action, p. 7). Claim 1 recites, "defining a candidate search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which one is chosen for each candidate model", while independent claims 6, 17, 19, 21, 23 and 26 use similar language, and claim 4 uses the term "features". The Office Action alleges that the specification does not specify how the value of n (the number of dimensions of the candidate model search space) is selected.

Applicant respectfully traverses this rejection. "N" refers to the number of sets of mutually exclusive features. One of ordinary skill in the art would understand how to choose "n"

number of dimensions. For example, a person skilled in the art of modeling might be interested in selecting a model to describe a given data set. In doing the analyses, the analyst will generate a number of questions and postulates. The analyst might be interested in examining the number of compartments in the pharmacokinetic model. They also might be interested in the relationship between age and the elimination rate constant (the elimination rate constant is the first order rate constant for transfer of drug out of the body). They also might be interested in the best model for residual variability. Other analyses and data sets may require examination of different questions, depending on what is known about the drug, and what questions are of interest. For each of there questions (e.g., number of compartments/relationship between elimination rate constant and age/best residual variability model) a set of mutually exclusive options can be created. For the number of compartments, there might be 1, 2 or 3. Exactly one of these must be chosen, the model must be either 1 or 2 or 3 compartments. It cannot be two of them (e.g., the model cannot be 1 and 2 compartments), and it must be some number of compartments. This set of features (1 or 2 or 3 compartments) is a mutually exclusive set. Similarly for the relationship between age and elimination rate constant, the analyst might postulate three relationships. These might be: No relationship, a linear relationship and an exponential relationship. Any model will include exactly one of these, a model cannot be both no relationship and a linear relationship, and it must be at exactly one of them, because they are mutually exclusive. Finally, for the residual error, the analyst might postulate two options, an additive and an exponential relationship. Again, exactly one of these must be chosen, having no residual variability is not an option, and having both is not an option. Thus, the number of dimensions, "n", (dimension is the same as a set of mutually exclusive features) is determined by the questions that the analyst determines should be addressed in the model, and will vary from one analysis to another. The described algorithm for model selection does not require a specific number of mutually exclusive set of features, it will work with any number from one to hundreds.

The Office Action further alleges that the specification does not provide a specific definition of a "feature", or indicate how mutually exclusive features are determined (Office Action, page 8).

Applicant respectfully traverses this rejection. It is correctly noted by the Examiner that a feature is the same as an effect. Applicant avers that the term "effect" is a standard term in

mixed effect modeling, as in the name of the standard software application – NONMEM (Non Linear Mixed Effect Modeling). As stated on page 8, line 7 of the specification, "The mixed effect part of the software refers to the combination of random and fixed effects". As noted by the office, effects can take may forms including, but not limited to interindividual variability, functions including logical parameters and other relationships. There are two broad categories of effects, fixed effects (those that are the same among all people) and random effects (those that vary between people). The nature of mixed effects modeling addresses both fixed and random effects in a single statistical model. One of skill in the art would be able to determine what effects should be considered in the candidate search space.

The office correctly notes that "the function describing the interindividual variability of each parameter' could mean many functions. So this means that features are a large set or items, may be 50 or 100 or more." In practice, the number of potential features (the candidate search space) is typically considerably larger than this. The large number of potential options for features/effects is the primary motivation for automated examination of those effects. For example, prior art models for pharmacokinetics and pharmacodynamics of new drugs often took weeks to months to build, precisely because of the large number of potential options and the complex interactions between the options. It should be noted that these models are typically required by the FDA in order to gain approval of new drugs. The prior art model building methods relied on labor intensive trial and error methods described in references IV, VI, VII and X listed in the specification. These references are provided in appendices B, C, D and E. The object of the invention is to provide methods for building models which achieve faster and more reliable results than the prior art methods. The nonlinear regression algorithm (e.g., that used in NONMEM) does not select the models, only estimates parameters for a given model and data set. It is the art and science of model building that gives rise to the large number of potential effects (e.g., effect of renal function on clearance), all combinations of which could be examined. The candidate models are selected based on knowledge of the biology of the system being modeled and principles of pharmacokinetics/pharmacodynamic model building. Identification of potential effects is an essential part of current model building practices. See references IV, VI, VII, X and XI cited in the specification and attached as appendices B, C, D, E and F. Accordingly, this rejection under 35 U.S.C. § 112, first paragraph may be properly withdrawn.

Claims 1-26 were rejected under 35 U.S.C. § 112, first paragraph. The Office Action alleges that the specification does not indicate how mutually exclusive features are determined.

Applicant respectfully traverses this reaction. Similarly to the definition of mutually exclusive set of features, the selection of the number of dimensions to be searched is standard current practice in model building. For example, for pharmacokinetics and pharmacodynamics, the selection of the number of dimension will depend on knowledge of the biology of the system and principles of pharmacokinetics/pharmacodynamics. See references IV, VI, VII, X and XI cited in the specification and attached as Appendices B, C, D, E and F.

The Office Action asks "Then what is achieved by grouping the features as sets of mutually exclusive features?" (Office Action, section 10.1) The grouping the features as mutually exclusive set permits the candidate space to be searched. Indeed the construction of models from different features requires that only one of a set of mutually exclusive feature be included. It is not possible to have a model that is both one and two compartment. Therefore, one and two compartments form a mutually exclusive set. Each feature (one compartment and two compartment) excludes the other. The candidate space is defined by all possible combinations of the features. The search of the candidate space is needed (as opposed to examining each feature in isolation) because frequently, probably usually, the same features in different combinations can have different properties. So, the effect of a1, in the combination (in the example given in the office communication) of a1, b1, c1...z1 will be different than the effect of a1 in the combination a1, b2, c2...z2. This is the nature of combinatorial optimization, to find the optimal or near optimal solution, it is not sufficient to examine each feature/effect in isolation. This lack of independence between different dimensions in the search space was formally demonstrated in reference xii (attached as Appenidx G. In the case of reference xii, the dimension included structural dimensions (e.g., number of compartments), statistical dimensions (random inter and intra individual variability) and covariate relationships.

Claim 2 stands rejected under 35 U.S.C. § 112, first paragraph. (Office Action, section 10.2). Claim 2 recites, "the candidate search space is searched for a near optimal or optimal model. According to the Office Action, the claim does not state what criteria are used to select an optimal or near optimal model, and asks what objective function is used.

Applicant respectfully traverses this rejection. The objective function is given on page 28 of the original application. Specifically, the objective function the sum of the log likelihood from NONMEM (see specification, page 28, line 20) with various penalties (costs) for other desirable qualities of the model. The definition of optimality, as used in this context is also given on page 15, lines 16 to 27. Accordingly, this rejection under 35 U.S.C. § 112, first paragraph may be properly withdrawn.

Claim 3 stands rejected under 35 U.S.C. § 112, first paragraph. Claim 3 recites, "the search is accomplished by a method selected from the group consisting of: full grid search, simulated annealing, integer programming, scatter search/path relinking, neural networks, tabu search and genetic algorithm." The Office Action asks what criteria are used to select one of the listed methods as the preferred method? (Office Action, section 10.3)

Applicant respectfully traverses this rejection. Claim 3 has been written as a standard Markush claim. The MPEP states that "Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of an alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B, and C." (MPEP 2173.05(h)). Any member of the Markush group specified in claim 3 can be selected to accomplish the search, and each search method is known is known to one of ordinary skill in the art. Applicants respectfully submit the specified Markush group does not present uncertainty or ambiguity with respect to the scope or clarity of the claims. Accordingly, this rejection may be properly withdrawn.

Claim 4 stands rejected under 35 U.S.C. § 112, first paragraph. Claim 4 recites, "selecting one feature from each of n sets of candidate features". The Office Action alleges that the claim does not state how one of the features is selected from each set of features – by random method or using some other rule (Office Action, section 10.4).

Claim 4 has been amended to clarify the process of generation of NONMEM/NMTRAN control files. Claim 4 no longer includes the selection of the features, but only the creation of a control file a list of selected features. The list of selected features consists of one feature from each set of mutually exclusive features. The method of selection of one feature from a list of

mutually exclusive feature depends on the algorithm used to search the candidate model space. In the case of genetic algorithm, the list of features is selected by randomly selecting "parents" with probability dependent on the fitness (see claim 6e). In the case of simulated annealing the selection is random. In the case of Tabu search the selection is deterministic. The step for generating the control file from the list of selected features is described on pages 31 to 34 of the specification. Accordingly, this rejection may be properly withdrawn.

Claim 5 stands rejected under 35 U.S.C. § 112, first paragraph. Claim 5 recites, "A method for automated evaluation of the optimality of a mode comprising: combining the log likelihood value with, optionally, a penalty for each parameter estimated, ...". The Office Action alleges that the claim dose not state how automated evaluation of the optimality of a model is achieved by combining log likelihood value with various penalties, and the determining the optimality of a model requires much more than combining log likelihood with various penalties, and that it is a more complex iterative process (Office Action, section 10.5).

Applicant respectfully traverses this rejection. This specification defines "optimality" as comprising:

"combining the log likelihood value (as output from NONMEM) with, optionally, a penalty for each parameter estimated (THETA in NONMEM), optionally, a penalty for each element of the interindividual variance matrix estimated (OMEGA in NONMEM), optionally, a penalty for each element of the intraindividual variance matrix estimated (SIGMA in NONMEM), optionally, a penalty imposed if the minimization does not conclude successfully, optionally, a penalty if the standard errors of the parameter estimates cannot be obtained (the covariance step in NONMEM), optionally, a penalty if the correlation matrix of the estimates (correlation matrix of estimate in NONMEM output) has any element > 0.95, and optionally a "niche" penalty for being similar to other models in the population (within a "niche radius" of other models)."

(Specification, page 15, line 17). Furthermore, one of skill in the art would understand how to determine evaluate optimality using log likelihood value and optional penalties for each parameter estimated. For example, references ix, xi and Practical Genetic Algorithms, Haupt et. al. John Wiley and Sons, New York, NY, 1998, pages 28-31, (attached hereto as Appendices H,

G and I) and other references are cited in the specification for optimality definitions, limited to numerical evaluations, without complex iterative processes. Accordingly, the rejection of claim 5 stands under 35 U.S.C. § 112, first paragraph, may be properly withdrawn.

Claim 6 stands rejected under 35 U.S.C. § 112, first paragraph. Claim 6 recites "each model is represented by a bit string". The Office Action alleges "there will be bits assigned to (a1, a2, a3) of a mutually exclusive set A, and that it is necessary to indicate how the bits are assigned to all the 75 features. Furthermore, the Office Action questions what is achieved by grouping the features as sets of mutually exclusive features and initially selecting only one feature from each set of mutually exclusive features?

Applicant respectfully traverses the rejection. The office action misinterpreted the assignment of bits to features. As noted on page 14, line 19 of the original application, the values in the bit strings are assigned to dimensions, not features. "The dimensions of the search space have discrete values." The algorithm described, of assigning bit strings to describe the model being evaluated is the standard genetic algorithm method and well known to those of skill in the art. (See, for example, Practical Genetic Algorithms, Haupt et. al. John Wiley and Sons, New York, NY, 1998, pages 25-27; attached as Appendix J). The Office Action alleges, "what you end up with is a random selection of features from this set of 75 features". That this process does not result in a random selection is evident from Figure 6, which shows gradual improvement in the fitness as the algorithm progress. If the selection were random, there would be no trend toward improvement. Accordingly, this rejection may be properly withdrawn.

IV. The Claims Meet the Requirements of 35 U.S.C. § 112, Second Paragraph.

Claims 6-17, 24 and 25 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." According to the Office Action, there is insufficient basis in claim 6 for "said population" as recited in the phrase "assessing the fitness of each model in said population. (Office Action, section 11.1).

Claim 6 has been amended to clarify that that the fitness of each candidate model is

assessed. Support for this amendment is found in original claim 6, part (a). Accordingly, this rejection under 35 U.S.C. § 112, second paragraph, may be properly withdrawn.

According to the Office Action, there is insufficient antecedent basis in claim 7 for the limitation "said initial population is a random population" (Office Action, section 11.1).

Claim 7 has been amended to clarify that said initial set of candidate models is randomly generated. Support for this amendment is found in original claims 6 and 7. Accordingly, this rejection under 35 U.S.C. § 112, second paragraph, may be properly withdrawn.

Claims 24 and 25 have been rejected under 35 U.S.C. § 112, second paragraph, as having insufficient antecedent basis for "reciting the method of claim 23 or 24, as claims 23 and 24 are directed to computer program products rather than to methods.

Claim 24 has been cancelled without prejudice. Claim 25 has been amended to recite "The computer program product of claim 24". Support for this amendment can be found in original claim 23. Accordingly, the rejection of claim 25 under 35 U.S.C. § 112, second paragraph, may be properly withdrawn.

Claims 1-3, 5, and 23-25 were rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps. Specifically, the Office Action alleges that to select a near optimal or optimal mathematical model from a set of candidate models, it is essential to specify an objective function for optimization and search the models using the objective function and select the model with the optimum value of the objective function (Office Action, sections 21.1 and 12.5).

Applicant respectfully disagrees that it is necessary to claim every feature of the invention, but for the sake of facilitating prosecution, claims 1, 5 and 23 have been amended to clarify that models are searched using an objective function to select the optimal or near optimal model, wherein said objective function is

$$Obj + theta\ \ penalty \cdot ntheta + random\ effect\ \ penalty \cdot nrand + success \cdot success\ \ penalty + covariance \cdot covariance\ \ penalty + correlation \cdot correlation\ \ penalty.$$

Support for these amendments can be found at page 28 of the application. Claims 2 and 24 have been cancelled without prejudice. Accordingly, the rejection of claims 1, 3, 5, 23 and 25 under 35 U.S.C. § 112, second paragraph, may be properly withdrawn.

Claims 3 and 25 have been rejected under 35 U.S.C. § 112, second paragraph for stating, "the search is accomplished by a method selected from the group consisting of: full grid search, simulated annealing, integer programming, scatter search/path relinking, neural networks, tabu search and genetic algorithm." According to the Office Action, it is necessary to specify which one of these search techniques is selected and what is the criteria for selecting on search procedure over another (Office Action, section 12.3).

Applicant respectfully traverses this rejection. As described above, claim 3 is a Markush claim. Markush claims express alternative limitations and are specifically permitted under MPEP 2173.05(h), and there is no requirement to specify which member of a Markush group is selected, not the criteria for selecting one member over another. For example claims 5 and 11 of Griffith (U.S. 6,197,575; cited by the Office Action) are Markush claims. Accordingly, the rejection of claims 3 and 25 under 35 U.S.C. § 112, second paragraph, may be properly withdrawn.

Claim 5 has been rejected under 35 U.S.C. § 112, second paragraph. Claim 5 recites "A method for automated evaluation of the optimality of a model comprising: combining the log likelihood value with, optionally, a penalty for each parameter estimated . . .". The Office Action alleges that the recited step will only provide a new definition of likelihood, rather than evaluating the optimality of a model, and that additional steps are required (Office Action, section 12.4).

Applicant respectfully traverses this rejection. Log likelihood is well described in the literature. The log likelihood function is -2 times the logarithm of the likelihood of the data occurring under the assumption(s) of the given model. Log likelihood does not include penalties for parameters, penalties for failing to estimate standard errors or having any off-diagonal elements of the correlation matrix > 0.95. The Akaike information criteria does include penalties for the number of parameters (references ix, cited in the specification and given in appendix H), but not the other penalties. This is not a new definition of log likelihood, *but a definition of*

optimality in this context. Accordingly, no additional steps are required. Specifically, this application defines "optimality" as comprising:

"combining the log likelihood value (as output from NONMEM) with, optionally, a penalty for each parameter estimated (THETA in NONMEM), optionally, a penalty for each element of the interindividual variance matrix estimated (OMEGA in NONMEM), optionally, a penalty for each element of the intraindividual variance matrix estimated (SIGMA in NONMEM), optionally, a penalty imposed if the minimization does not conclude successfully, optionally, a penalty if the standard errors of the parameter estimates cannot be obtained (the covariance step in NONMEM), optionally, a penalty if the correlation matrix of the estimates (correlation matrix of estimate in NONMEM output) has any element > 0.95, and optionally a "niche" penalty for being similar to other models in the population (within a "niche radius" of other models)."

(page 15, line 17). References cited in the specification for other optimality definitions include references IX, disclosed in the specification and attached hereto as Appendices H. Accordingly, this rejection of claim 5 under 35 U.S.C. § 112, second paragraph may be properly withdrawn.

V. The Claims Meet the Requirements of 35 U.S.C. § 101.

Claims 1-3 and 6-20 stand rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. The Examiner indicated that claims 1-3, 6-16, 17-18 and 19-20 would be statutory if independent claims 1, 6, 17, and 19 were written as "A computer implemented method for selecting a near optimal or optimal mathematical model form a set of candidate models". Applicants are grateful for the suggestion, and have amended independent claims 1, 6, 17 and 19, as recommended by the Examiner. Claim 2 has been cancelled without prejudice. Accordingly, the rejection of claims 1, 3 and 4-20 under 35 U.S.C. § 101 may be properly withdrawn.

Claims 23-25 stand rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. The Examiner indicated that claims 23-25 would be statutory if independent claim 23 were written as "A computer program product comprising a computer usable storage medium having computer-readable instructions which when executed on a

computer perform a process for selecting a near optimal or optimal mathematical model form a set of candidate models, the computer readable instructions comprising:". Applicants are have amended independent claim 23 as suggested by the Examiner. Claim 24 has been cancelled without prejudice. Accordingly, the rejection of claims 23 and 25 under 35 U.S.C. § 101 may be properly withdrawn.

Claim 26 stands rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. The Examiner indicated that claim 26 would be statutory if it were written as "A computer program product comprising a computer usable storage medium having computer-readable instructions which when executed on a computer perform a process for selecting a near optimal or optimal mathematical model form a set of candidate models, wherein the computer readable instructions are configured to:". Applicants have amended claim 26 as suggested by the Examiner. Accordingly, the rejection of claim 26 under 35 U.S.C. § 101 may be properly withdrawn.

VI. The Claims Meet the Requirements of 35 U.S.C. § 102.

Claims 1-2 and 23-24 stand rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Cahill (U.S. Patent application 2002/0196975). (Office Action, p.21).

Applicant respectfully traverses this rejection. The instant application was filed 11 June 2001 (10 June 2001 fell on a Sunday), and claims the benefit of priority to U.S. provisional application 60/210,672, filed 10 June 2000. Priority to this provisional application was acknowledged by the Office Action at page 2. Cahill was filed on 12 April 2001, after the priority date of the instant application. Thus, Cahill is not a proper 102(e) reference and does not constitute prior art to the instant invention. Accordingly, the rejection of claims 1-2 and 23-24 under 35 U.S.C. §102(e) may be properly withdrawn.

VII. The Claims Meet the Requirements of 35 U.S.C. § 103.

Applicant addresses all of the rejections under 35 U.S.C. §103(a) together, as they all rely on Cahill, which as stated above is not a proper prior art reference. Specifically, the Office

Action rejected claims 3 and 25 under 35 U.S.C. §103(a) as being unpatentable over Cahill (U.S. Patent Application 2002/0196975) in view of Walser (U.S. Patent 6,031,984), and further in view of Rothberg (U.S. Patent 6,432,361), Lee (U.S. Patent 6,530,873) and Phillips (U.S. Patent 6,792,399) (Office Action, page 23).

Claim 5 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Cahill in view of Thomas (U.S. Patent 5,857,462) (Office Action, page 25).

Claims 6-8, 11-12 and 26 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Cahill in view of Handa (U.S. Patent 5,465,218), and further in view of Lee (Office Action, page 27).

Claim 9 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Cahill in view of Handa (U.S. Patent 5,465,218), and further in view of Lee and Hottinen (U.S. Patent 6,449,266) (Office Action, page 35).

Claim 15 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Cahill in view of Handa, and further in view of Lee, Griffith (U.S. patent 6,197,575) and Reznik (U.S. Patent 6,368,813) (Office Action, page 36).

Claims 17 and 19 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Cahill in view of Rothberg (U.S. Patent 6,432,361) (Office Action, page 37).

Applicant respectfully traverse all of the rejections under 35 U.S.C. §103(a). All of the above rejections for obviousness depend upon Cahill. As stated above, the instant application was filed 11 June 2001 (10 June 2001 fell on a Sunday), and claims the benefit of priority to U.S. provisional application 60/210,672, filed 10 June 2000. Priority to this provisional application was acknowledged by the Office Action at page 2. Cahill was filed on 12 April 2001, after the priority date of the instant application. Thus, Cahill is not a proper 102(e) reference and does not constitute prior art to the instant invention. In addition, Rothberg was filed on 28 November 2000, which is after the 10June 2000 priority date of the instant application. Therefore, Rothberg is not a proper prior art reference. Accordingly, the rejection of claims 3, 5-9, 11-12, 15, 17, 19 and 25-26 and 23-24 under 35 U.S.C. §103(a) may be properly withdrawn.

does not result in a random selection is evident from Figure 6, which shows gradual improvement in the fitness as the algorithm progress. If the selection were random, there would be no trend toward improvement. Accordingly, this rejection may be properly withdrawn.

IV. The Claims Meet the Requirements of 35 U.S.C. § 112, Second Paragraph.

Claims 6-17, 24 and 25 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." According to the Office Action, there is insufficient basis in claim 6 for "said population" as recited in the phrase "assessing the fitness of each model in said population. (Office Action, section 11.1).

Claim 6 has been amended to clarify that that the fitness of each candidate model is assessed. Support for this amendment is found in original claim 6, part (a). Accordingly, this rejection under 35 U.S.C. § 112, second paragraph, may be properly withdrawn.

According to the Office Action, there is insufficient antecedent basis in claim 7 for the limitation "said initial population is a random population" (Office Action, section 11.1).

Claim 7 has been amended to clarify that said initial set of candidate models is randomly generated. Support for this amendment is found in original claims 6 and 7. Accordingly, this rejection under 35 U.S.C. § 112, second paragraph, may be properly withdrawn.

Claims 24 and 25 have been rejected under 35 U.S.C. § 112, second paragraph, as having insufficient antecedent basis for "reciting the method of claim 23 or 24, as claims 23 and 24 are directed to computer program products rather than to methods.

Claim 24 has been cancelled without prejudice. Claim 25 has been amended to recite "The computer program product of claim 24". Support for this amendment can be found in original claim 23. Accordingly, the rejection of claim 25 under 35 U.S.C. § 112, second paragraph, may be properly withdrawn.

Claims 1-3, 5, and 23-25 were rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps. Specifically, the Office Action alleges that to

select a near optimal or optimal mathematical model from a set of candidate models, it is essential to specify an objective function for optimization and search the models using the objective function and select the model with the optimum value of the objective function (Office Action, sections 21.1 and 12.5).

Applicant respectfully disagrees that it is necessary to claim every feature of the invention, but for the sake of facilitating prosecution, claims 1, 5 and 23 have been amended to clarify that models are searched using an objective function to select the optimal or near optimal model, wherein said objective function is

$$Obj + theta\ penalty \cdot ntheta + random\ effect\ penalty \cdot nrand + success \cdot success\ penalty + covariance \cdot covariance\ penalty + correlation \cdot correlation\ penalty.$$

Support for these amendments can be found at page 28 of the application. Claims 2 and 24 have been cancelled without prejudice. Accordingly, the rejection of claims 1, 3, 5, 23 and 25 under 35 U.S.C. § 112, second paragraph, may be properly withdrawn.

Claims 3 and 25 have been rejected under 35 U.S.C. § 112, second paragraph for stating, "the search is accomplished by a method selected from the group consisting of: full grid search, simulated annealing, integer programming, scatter search/path relinking, neural networks, tabu search and genetic algorithm." According to the Office Action, it is necessary to specify which one of these search techniques is selected and what is the criteria for selecting on search procedure over another (Office Action, section 12.3).

Applicant respectfully traverses this rejection. As described above, claim 3 is a Markush claim. Markush claims express alternative limitations and are specifically permitted under MPEP 2173.05(h), and there is no requirement to specify which member of a Markush group is selected, not the criteria for selecting one member over another. For example claims 5 and 11 of Griffith (U.S. 6,197,575; cited by the Office Action) are Markush claims. Accordingly, the rejection of claims 3 and 25 under 35 U.S.C. § 112, second paragraph, may be properly withdrawn.

Claim 5 has been rejected under 35 U.S.C. § 112, second paragraph. Claim 5 recites "A

method for automated evaluation of the optimality of a model comprising: combining the log likelihood value with, optionally, a penalty for each parameter estimated . . .". The Office Action alleges that the recited step will only provide a new definition of likelihood, rather than evaluating the optimality of a model, and that additional steps are required (Office Action, section 12.4).

Applicant respectfully traverses this rejection. Log likelihood is well described in the literature. The log likelihood function is -2 times the logarithm of the likelihood of the data occurring under the assumption(s) of the given model. Log likelihood does not include penalties for parameters, penalties for failing to estimate standard errors or having any off-diagonal elements of the correlation matrix > 0.95. The Akaike information criteria does include penalties for the number of parameters (references ix, cited in the specification and given in appendix H), but not the other penalties. This is not a new definition of log likelihood, *but a definition of optimality* in this context. Accordingly, no additional steps are required. Specifically, this application defines "optimality" as comprising:

"combining the log likelihood value (as output from NONMEM) with, optionally, a penalty for each parameter estimated (THETA in NONMEM), optionally, a penalty for each element of the interindividual variance matrix estimated (OMEGA in NONMEM), optionally, a penalty for each element of the intraindividual variance matrix estimated (SIGMA in NONMEM), optionally, a penalty imposed if the minimization does not conclude successfully, optionally, a penalty if the standard errors of the parameter estimates cannot be obtained (the covariance step in NONMEM), optionally, a penalty if the correlation matrix of the estimates (correlation matrix of estimate in NONMEM output) has any element > 0.95, and optionally a "niche" penalty for being similar to other models in the population (within a "niche radius" of other models)."

(page 15, line 17). References cited in the specification for other optimality definitions include references IX, disclosed in the specification and attached hereto as Appendices H. Accordingly, this rejection of claim 5 under 35 U.S.C. § 112, second paragraph may be properly withdrawn.

V. The Claims Meet the Requirements of 35 U.S.C. § 101.

Claims 1-3 and 6-20 stand rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. The Examiner indicated that claims 1-3, 6-16, 17-18 and 19-20 would be statutory if independent claims 1, 6, 17, and 19 were written as "A computer implemented method for selecting a near optimal or optimal mathematical model form a set of candidate models". Applicants are grateful for the suggestion, and have amended independent claims 1, 6, 17 and 19, as recommended by the Examiner. Claim 2 has been cancelled without prejudice. Accordingly, the rejection of claims 1, 3 and 4-20 under 35 U.S.C. § 101 may be properly withdrawn.

Claims 23-25 stand rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. The Examiner indicated that claims 23-25 would be statutory if independent claim 23 were written as "A computer program product comprising a computer usable storage medium having computer-readable instructions which when executed on a computer perform a process for selecting a near optimal or optimal mathematical model form a set of candidate models, the computer readable instructions comprising:". Applicants are have amended independent claim 23 as suggested by the Examiner. Claim 24 has been cancelled without prejudice. Accordingly, the rejection of claims 23 and 25 under 35 U.S.C. § 101 may be properly withdrawn.

Claim 26 stands rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. The Examiner indicated that claim 26 would be statutory if it were written as "A computer program product comprising a computer usable storage medium having computer-readable instructions which when executed on a computer perform a process for selecting a near optimal or optimal mathematical model form a set of candidate models, wherein the computer readable instructions are configured to:". Applicants have amended claim 26 as suggested by the Examiner. Accordingly, the rejection of claim 26 under 35 U.S.C. § 101 may be properly withdrawn.

VI. The Claims Meet the Requirements of 35 U.S.C. § 102.

Claims 1-2 and 23-24 stand rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Cahill (U.S. Patent application 2002/0196975). (Office Action, p.21).

Applicant respectfully traverses this rejection. The instant application was filed 11 June 2001 (10 June 2001 fell on a Sunday), and claims the benefit of priority to U.S. provisional application 60/210,672, filed 10 June 2000. Priority to this provisional application was acknowledged by the Office Action at page 2. Cahill was filed on 12 April 2001, after the priority date of the instant application. Thus, Cahill is not a proper 102(e) reference and does not constitute prior art to the instant invention. Accordingly, the rejection of claims 1-2 and 23-24 under 35 U.S.C. §102(e) may be properly withdrawn.

VII. The Claims Meet the Requirements of 35 U.S.C. § 103.

Applicant addresses all of the rejections under 35 U.S.C. §103(a) together, as they all rely on Cahill, which as stated above is not a proper prior art reference. Specifically, the Office Action rejected claims 3 and 25 under 35 U.S.C. §103(a) as being unpatentable over Cahill (U.S. Patent Application 2002/0196975) in view of Walser (U.S. Patent 6,031,984), and further in view of Rothberg (U.S. Patent 6,432,361), Lee (U.S. Patent 6,530,873) and Phillips (U.S. Patent 6,792,399) (Office Action, page 23).

Claim 5 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Cahill in view of Thomas (U.S. Patent 5,857,462) (Office Action, page 25).

Claims 6-8, 11-12 and 26 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Cahill in view of Handa (U.S. Patent 5,465,218), and further in view of Lee (Office Action, page 27).

Claim 9 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Cahill in view of Handa (U.S. Patent 5,465,218), and further in view of Lee and Hottinen (U.S. Patent 6,449,266) (Office Action, page 35).

Claim 15 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Cahill in

view of Handa, and further in view of Lee, Griffith (U.S. patent 6,197,575) and Reznik (U.S. Patent 6,368,813) (Office Action, page 36).

Claims 17 and 19 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Cahill in view of Rothberg (U.S. Patent 6,432,361) (Office Action, page 37).

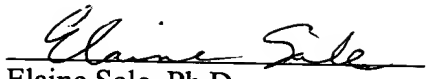
Applicant respectfully traverse all of the rejections under 35 U.S.C. §103(a). All of the above rejections for obviousness depend upon Cahill. As stated above, the instant application was filed 11 June 2001 (10 June 2001 fell on a Sunday), and claims the benefit of priority to U.S. provisional application 60/210,672, filed 10 June 2000. Priority to this provisional application was acknowledged by the Office Action at page 2. Cahill was filed on 12 April 2001, after the priority date of the instant application. Thus, Cahill is not a proper 102(e) reference and does not constitute prior art to the instant invention. In addition, Rothberg was filed on 28 November 2000, which is after the 10June 2000 priority date of the instant application. Therefore, Rothberg is not a proper prior art reference. Accordingly, the rejection of claims 3, 5-9, 11-12, 15, 17, 19 and 25-26 and 23-24 under 35 U.S.C. §103(a) may be properly withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance. However, if the Examiner believes that any further discussion of this communication would be helpful, he is encouraged to contact the undersigned by telephone.

A Petition for a one (1) month Extension of Time under 37 C.F.R. § 1.136(a) is filed concurrently herewith, which extends the response period from February 19, 2005 to March 19, 2005, which falls on a Saturday. A credit card form authorizing payment of the $60.00 fee for the one month extension of time is provided herewith. No other fees are believed due at this time. However, Applicant authorizes the payment of any other fee that may be due to the credit card designated on the credit card authorization form.

Respectfully submitted,



Elaine Sale, Ph.D.
Attorney for Applicant
Registration No. 41,286

Date: March 21, 2005

1013 Dickinson Cir.
Raleigh, NC 27614

Tel: (919) 287-6332
Fax: (919) 287-6301